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Original Article

Lung cancer occurrence attributable to passive smoking among never smokers in China: a systematic review and meta-analysis

Yihui Du[1], Xiaonan Cui[2,3], Grigory Sidorenkov[1], Harry J. M. Groen[4], Rozemarijn Vliegenthart[2], Marjolein A. Heuvelmans[1,5], Shiyuan Liu[6], Matthijs Oudkerk[7], Geertruida H. de Bock[1]

[1]Department of Epidemiology, [2]Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [3]Department of Radiology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Centre of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, China; [4]Department of Pulmonary Diseases, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands; [5]Department of Pulmonology, Medisch Spectrum Twente, Enschede, The Netherlands; [6]Department of Radiology, Shanghai Changzheng Hospital, The Second Military Medical University Shanghai, Shanghai 200003, China; [7]University of Groningen, Groningen, The Netherlands

Contributions: (I) Conception and design: Y Du, G Sidorenkov, HJM Groen, R Vliegenthart, MA Heuvelmans, S Liu, M Oudkerk, GH de Bock; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Y Du, X Cui, G Sidorenkov, S Liu, GH de Bock; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Geertruida H. de Bock. Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, PO Box 30.001, FA 40, 9700 RB Groningen, The Netherlands. Email: g.h.de.bock@umcg.nl.

Background: Quantifying the occurrence of lung cancer due to passive smoking is a necessary step when forming public health policy. In this study, we estimated the proportion of lung cancer cases attributable to passive smoking among never smokers in China.

Methods: Six databases were searched up to July 2019 for original observational studies reporting relative risks (RRs) or odds ratios (ORs) for the occurrence of lung cancer associated with passive smoking in Chinese never smokers. The population attributable fraction (PAF) was then calculated using the combined proportion of lung cancer cases exposed to passive smoking and the pooled ORs from meta-analysis. Data are reported with their 95% confidence intervals.

Results: We identified 31 case-control studies of never smokers and no cohort studies. These comprised 9,614 lung cancer cases and 13,093 controls. The overall percentages of lung cancers attributable to passive smoking among never smokers were 15.5% (9.0–21.4%) for 9 population-based studies and 22.7% (16.6–28.3%) for 22 hospital-based studies. The PAFs for women were 17.9% (11.4–24.0%) for the population-based studies and 20.9% (14.7–26.7%) for the hospital-based studies. The PAF for men was only calculable for hospital-based studies, which was 29.0% (95% CI: 8.0–45.2%). Among women, the percentage of lung cancer cases attributable to household exposure (19.5%) was much higher than that due to workplace exposure (7.2%).

Conclusions: We conclude that approximately 16% of lung cancer cases among never smokers in China are potentially attributable to passive smoking. This is slightly higher among women (around 18%), with most cases occurring due to household exposure.

Keywords: Population attributable fraction (PAF); environmental tobacco smoke; passive smoking; secondhand smoke; lung cancer

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Introduction

Environmental tobacco smoke is a common source of indoor air pollution worldwide (1,2), and its inhalation is known as passive smoking. Importantly, the International Agency for Research on Cancer has stated that passive smoking exposes people to the same carcinogens as active smoking, which is the leading cause of lung cancer (3). Consequently, passive smoking is considered an important cause of lung cancer in never smokers (3,4), increasing their risk of the disease (5). The biological plausibility for this association is that carcinogens and toxic substances seem to remain present in side-stream smoke and exhaled mainstream smoke (6-8).

Exposure to passive smoking continues to be a major public health concern, resulting in a large economic burden worldwide, including in China (1,9). Worldwide, it is estimated that 40% of children, 33% of males, and 35% of females identified as never smokers are exposed to passive smoking. The situation in China is complicated by having more tobacco consumers than any other country, with 316 million current smokers exposing more than 50% of never smokers to passive smoking in the home and workplace in 2015 (10). Depending on the study, estimates indicate that exposure to passive smoke in China varies from 34.1% to 72.4% (11-15). This wide range can be explained by variations in age and sex, as well as the region, source, and definition of exposure. Nevertheless, the large number of smokers necessitates that we quantify the effect of smoking on never smokers in the Chinese population to guide public health decisions.

In this systematic review, we aimed to estimate the proportion of lung cancers in never smokers that could be deemed attributable to passive smoking. To do so, we estimated the expected proportional reduction in lung cancer occurrence as if there had been no exposure to passive smoking, the so-called population attributable fraction (PAF) (16), assuming a causal relationship between passive smoking and lung cancer.

Methods

Data sources and search strategy

We conducted a comprehensive search of six databases for publications in English or Chinese in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (17). Articles published in English were identified through the PubMed and Web of Science databases. Those published in Chinese were found through the China National Knowledge Infrastructure, Database of Chinese Scientific & Technical Periodicals, Wan Fang database, and the China Biology Medical literature database.

All databases were searched from inception to July 2019 to identify original observational studies that reported relative risks (RRs) or odds ratios (ORs) of the association between passive smoking and lung cancer in Chinese never smokers. The following search terms were used: "tobacco smoke," "secondhand smoking," "passive smoking," "lung cancer," "China," and "Chinese." A detailed summary of the search strategy used in each database is described in *Table S1*. Additionally, we manually searched the reference lists of retrieved articles to identify relevant studies that were not revealed by the database search.

Eligibility criteria and study selection

Studies were included in the systematic review if they met the following criteria: participants were never smokers from China (including Taiwan), passive smoking was assessed at an individual level, risk estimates were reported for the occurrence of primary lung cancer, and a case-control or cohort design was used. Studies were excluded for the following reasons: if they focused on a specific occupational population (e.g., miners, catering workers, textile workers, oil field workers, or those exposed to asbestos or nuclear fuel); if they included residents of Xuanwei County of Yunnan Province [residents in this area have exceptionally high exposure to residential smoky coal emissions, which is associated with a 36-fold increase in lung cancer mortality in men and a 99-fold increase in women compared with smokeless coal (18)]; if the outcome of interest was the specific mortality instead of the occurrence of lung cancer; and if the proportion of primary lung cancer cases exposed to passive smoking was unavailable to calculate PAF. In the event of multiple publications from a single study, the most recent publication was selected.

Three reviewers independently screened the identified studies for inclusion. YD screened all studies, GS screened those published in English, and XC screened those published in Chinese. After a calibration session, any disagreement was mediated by a fourth reviewer (GHdB for the studies published in English and SL for the studies published in Chinese).

Data extraction and quality assessment

One author (Y Du) extracted data using a standardized extraction sheet (*Figure S1*) and two co-authors (G Sidorenkov, X Cui) reviewed the data. For each selected publication, three reviewers (Y Du, G Sidorenkov, X Cui) independently assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS) (19). The NOS is a methodological assessment tool recommended for use with cohort and case-control studies that uses a star-based scale ranging from 0 to 9 stars (20). Quality is assessed on three domains in the NOS: (I) study group selection; (II) group comparability; and (III) exposure/outcome reliability. The comparability assessment needed to be further specified based on the topic of the analysis, which was done in a consensus meeting among the authors before assessing the studies. It was agreed that one star would be given when the comparison between cases and controls was adjusted for age and sex. Another star was given when there was adjustment for at least one of the following confounders: radon, asbestos, family history of lung cancer and cooking smoke. Any disagreements were settled by consensus or were adjudicated by a third reviewer (GHdB/SL). Studies assessed as zero points for the comparability domain were excluded from the meta-analysis.

Data analyses and syntheses

The first step involved a meta-analysis of the OR and corresponding 95% confidence intervals (CIs), using a random effects model. We performed I^2 tests and considered data to have heterogeneity when the I^2 value was >50%. For studies that reported both crude and adjusted OR estimates, the adjusted risk estimate was selected for the meta-analysis. For studies that reported stratified ORs, the overall OR was calculated by combing the stratified ORs and using them in the subgroup PAF calculations, as applicable. For studies that did not report OR directly, but where the necessary data were available, we performed the OR calculation ourselves. The derivation of the ORs used in the study, together with their matched/adjusted factors in each included study, are presented in *Table S2*. To evaluate the robustness of the pooled ORs, we performed sensitivity analyses in which each study was sequentially removed and the OR was recalculated. Publication bias was tested using Begg's test and a funnel plot.

The next step involved calculating the point estimate of PAF based on the pooled proportion of exposed cases and the pooled OR (16,21), using the following formula:

$$PAF = P_c \frac{RR-1}{RR}$$

where pc is the percentage of cases exposed in the combined population.

RR was replaced with the OR (as an approximation of the RR) for case-control studies (16). The 95% CI of the PAF was then estimated according to a formula described elsewhere, in which the variance of both the OR and the exposed cases were considered (21):

The variance of PAF is $var\left[\ln\left(1-PAF\right)\right] = \left[\frac{PAF^2}{\left(1-PAF\right)^2}\right] * \left\{\left[\frac{var\ln\left(RR\right)}{\left(RR-1\right)^2}\right] + \left[\frac{2}{n_{exp-cases} * \left(RR-1\right)}\right] + \left(\frac{n_{nonexp-cases}}{n_{exp-cases} * n_{cases}}\right)\right\}$

The corresponding limits of ln(1-*PAF*) are $\ln\left(1-PAF\right) +/- 1.96 * \left\{\sqrt{var\left[\ln\left(1-PAF\right)\right]}\right\}$.

The upper limit (UL) and lower limit (LL) of PAF were calculated as 1-exp{*LL*[ln(1-*PAF*)]} and 1-exp{*UL*[ln(1-*PAF*)], respectively.

The meta-analysis was performed using Stata/SE software, version 15.0 (StataCorp., college Station, TX; package "pr0012"), and the PAF estimations were performed using Microsoft Excel 2010 (Microsoft Corporation, Washington).

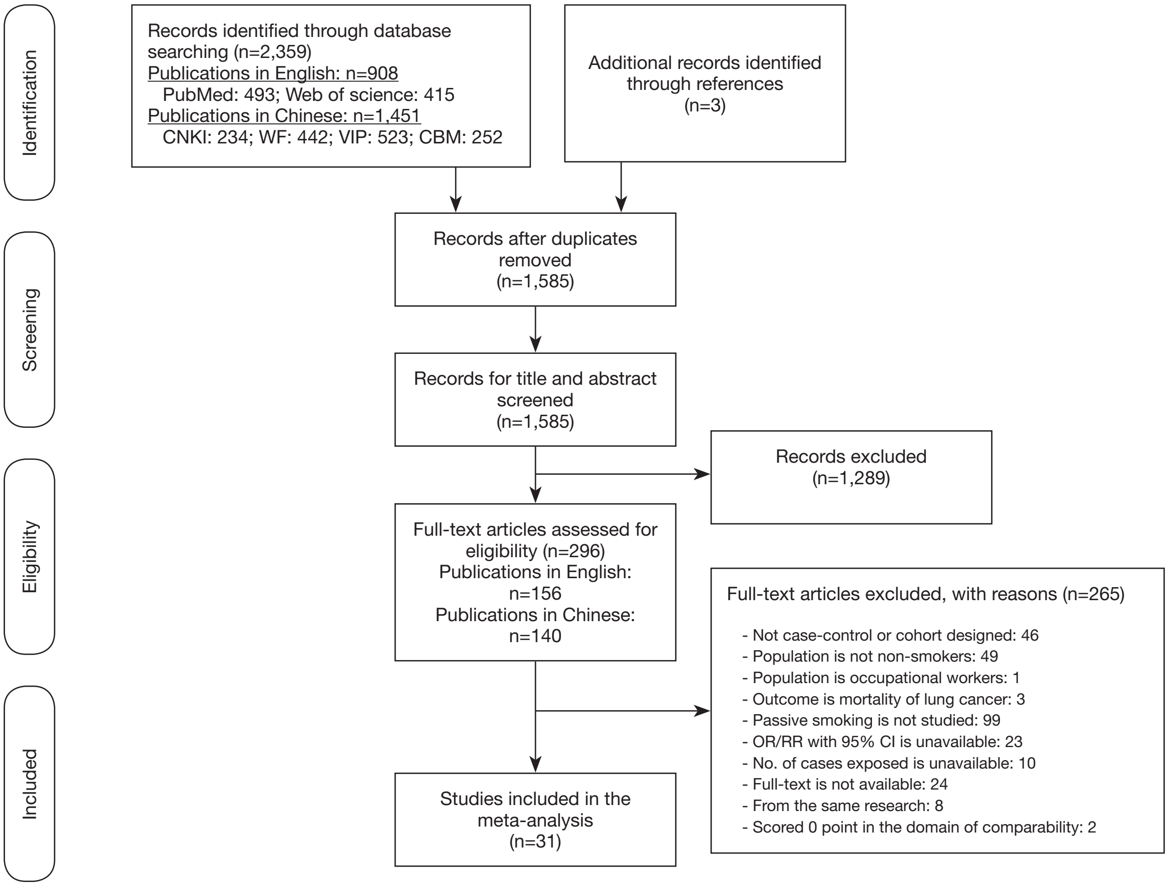

Figure 1 Selection of studies for inclusion in the systematic review. CBM, and the China Biology Medical literature database; CNKI, China National Knowledge Infrastructure; VIP, Database of Chinese Scientific & Technical Periodicals; WF, Wan Fang database.

Results

Eligible studies and their characteristics

We identified 2,359 articles from the six databases we searched and retrieved 296 papers for full-text review; of these, 31 case-control studies [22 published in English (22-43) and 9 published in Chinese (44-52)] were eligible for inclusion (*Figure 1*). No cohort studies fulfilled the inclusion criteria. The details of all included studies are summarized in *Table 1*.

The average methodological quality score was 6.0±0.9, ranging from 5 to 8 (≥7 for 9 studies). Details of the quality assessment are presented in *Table S3*. Concerning exposure ascertainment, 29 studies had no blinding to the case/control status during interviews. Notably, the definitions of never smoker and passive smoking varied across the studies, as presented in *Table S4*.

Among the eligible studies, 9,614 cases of lung cancer and 13,093 controls were included, with exposure to passive smoking in 5,923 (61.6%) and 7,089 (54.1%), respectively. Overall, 11 studies included both men and women, 19 studies included only women, and 1 study included only men. The age of the population of interest in the included studies varied and was presented either as mean and standard deviation or percentage, as shown in *Table 1*. Most studies (n=22) were conducted in mainland China. The control groups were recruited from a hospital in 22 studies, but they were population-based in the remaining 9 studies. All but 5 studies, which were limited to lung adenocarcinoma, included all types of lung cancer. Of the 20 studies that provided data on the source of passive smoking, 18 considered both home and work exposure, 2 considered home exposure only, and 1 considered work exposure only.

Table 1 Characteristics of the eligible studies included in the systematic review and meta-analysis

Study	Sex	Age	Study period	Region	Cases	Controls	Setting	Cancer type	Exposure source	Exposure age	NOS score
TH Lam 1987	F	Cases: 65.6±11.2; Controls: 65.3±10.9	1983–1986	Non-mainland	199	335	PB	All types	Home	NA	7
LC Koo 1987	F	Cases: 57.8±1.81; Controls: 59.3±9.94	1981–1983	Non-mainland	88	137	PB	All types	Home/work	Child/adult	5
Q Liu 1993	F	NA	1983.06–1984.06	Mainland	38	69	HB	All types	Home	NA	6
X Sun 1995†	F	30–69 years. Cases: 53.3; Controls: 54.9	1985.01–1991.12	Mainland	230	230	HB	All types	Home/work	NA	5
S Zheng 1997†	F + M	NA	1990.01–1993.12	Mainland	94	259	PB	All types	NA	NA	6
L Zhong 1999	F	35–69 years	1992.02–1994.01	Mainland	504	601	PB	All types	Home/work	Child/adult	8
L Wang 2000	F + M	30–75 years	1994.01–1998.04	Mainland	228	521	PB	All types	NA	Child/adult	7
CH Lee 2000	F	Cases: 61.5±12.2; Controls: 61.2±11.5	1992.01–1998.01	Non-mainland	268	445	HB	All types	Home/work	Child/adult	7
YC Ko 2000	F	41–70 years. Cases: 73.3%; Controls: 75.4%	1993–1996	Non-mainland	131	514	HB	All types	Home/work	Child/adult	6
E Liu 2001†	F	35–69 years	1992.02–1993.12	Mainland	498	595	PB	All types	Work	NA	7
M Chan-Yeung 2003	F + M	NA	1999.05–2001.12	Non-mainland	158	209	HB	All types	Home/work	NA	6
M Li 2005†	F	NA	2002.01–2004.10	Mainland	126	126	HB	AC	NA	NA	5
IT Yu 2006	F	30–79 years. Cases: 64.1 Controls: 63.3	2002.07–2004.06	Non-mainland	200	285	PB	All types	Home/work	NA	5
J Fang 2006†	F	18–70 years	2001.09–2004.02	Mainland	157	214	HB	All types	Home/work	NA	5
C Galeone 2008	F + M	NA	1987.05–1990.05	Mainland	60	216	HB	All types	Home/work	NA	6
LA Tse 2009	M	35–79 years	2004.02–2006.09	Non-mainland	132	536	PB	All types	Home/work	NA	7
T Jiang 2010†	F + M	Cases: 55.56±11.79; Controls: 55.67±11.67	2009.03–2009.12	Mainland	145	145	HB	All types	NA	NA	7
M Huang 2011†	F + M	40–60 years. Cases: 53.58%; Controls: 46.95%	2006.12–2010.01	Mainland	293	475	HB	All types	Home/work	NA	5
L Mu 2013	F + M	45–64 years. Cases: 51.88%; Controls: 54.72%	2005–2007	Mainland	178	283	HB	All types	Home/work	NA	6
YW Ren 2013	F	Cases: 56.47±11.28; Controls: 56.04±12.11	2002.01–2012.12	Mainland	764	983	HB	AC	Home/work	NA	5

Table 1 (*continued*)

Table 1 (*continued*)

Study	Sex	Age	Study period	Region	Cases	Controls	Setting	Cancer type	Exposure source	Exposure age	NOS score
YL Lo 2013	F + M	≥01 years. Cases: 58.38±11.66; Controls: 58.94±11.70	2002.09–2009.04	Non-mainland	1,540	1,540	HB	All types	home/work	NA	7
X Xue 2013	F	Cases: 53.05±4.48; Controls: 53.61±4.13	2002.01–2008.01	Mainland	410	410	HB	AC	NA	NA	6
Z Yin 2014	F	Cases: 56.1±11.9; Controls: 56.8±11.1	2004.01–2010.11	Mainland	306	318	HB	All types	NA	NA	5
S Li 2014	F	Cases: 55.7±11.6; Controls: 56.6±11.0	2002.01–2012.11	Mainland	242	277	HB	AC	NA	NA	6
J Pan 2014 a	F	28–80 years. Cases: 60.21±10.17 Controls: 59.97±10.36	2005.11–2008.12	Mainland	229	458	PB	All types	NA	NA	6
L Yang 2015	F + M	Cases: ≤60: 50.8%; >60: 49.2%. Controls: ≤60: 50.6%; >60:49.4%	2002–2011	Mainland	735	914	HB	All types	Home/work	NA	7
Z Liu 2015[†]	F + M	NA	2006.01–2013.12	Mainland	480	794	HB	All types	Home/work	NA	6
X Fang 2016	F	Cases: 56.26±11.71; Controls: 53.13±11.64	NA	Mainland	224	244	HB	All types	NA	NA	5
L Han 2017	F + M	>18 years. Cases: 58.1±7.5; Controls: 57.5±5.0	Cases: 2006–2015, Controls: 2013.05–2015.02	Non-mainland	351	344	HB	AC	Home/work	NA	5
J Pan 2018	F	Cases: 54.4±10.0; Controls: 54.7±9.5	2014.01–2016.01	Mainland	261	265	HB	All types	NA	NA	6
R Qu 2019	F	Cases: 56.9±10.3; Controls: 58.0±10.7	2010.08–2013.02	Mainland	345	351	HB	All types	NA	NA	5

[†], study published in Chinese. AC, adenocarcinoma; HB, hospital-based; NA, not available; NOS, Newcastle-Ottawa Scale; PB, population-based.

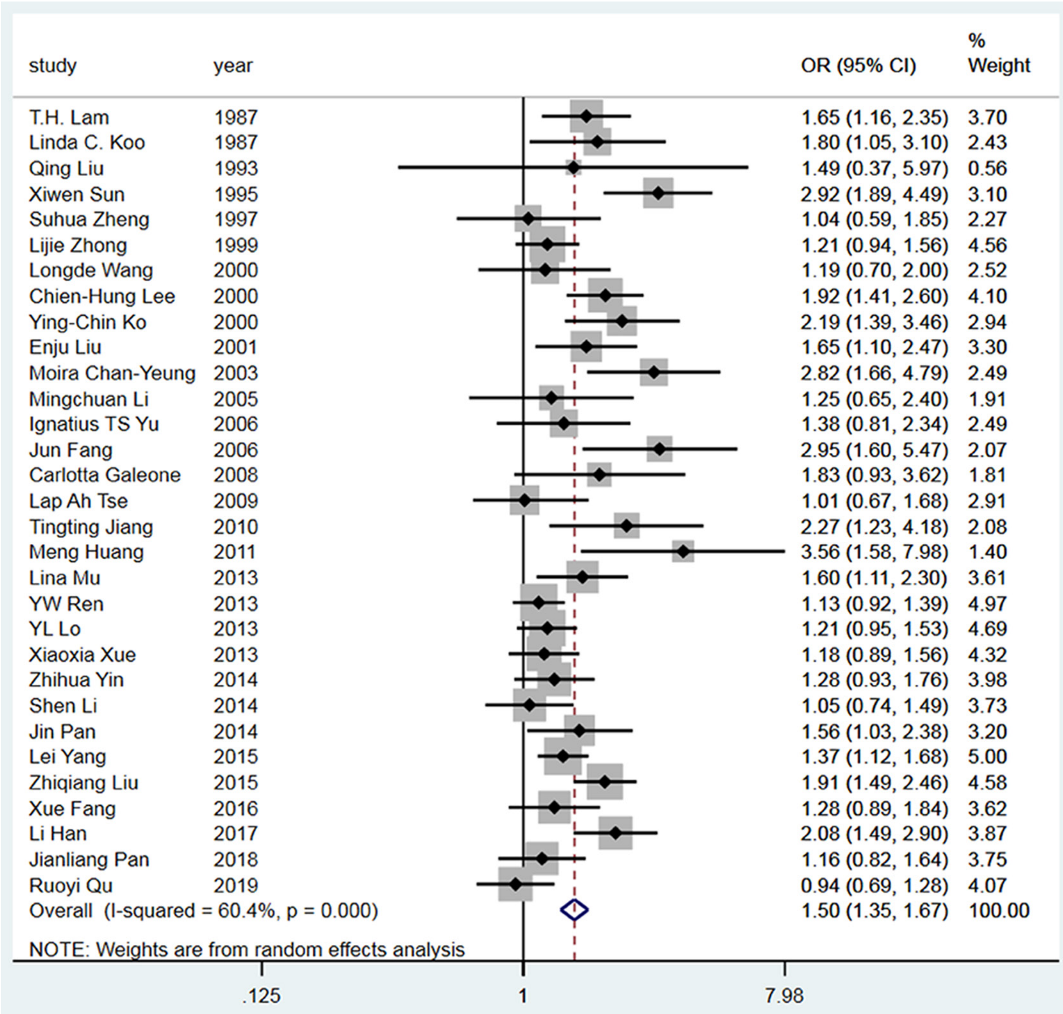

Figure 2 Forest plot of the random effects meta-analysis for the association between passive smoking and lung cancer among never smokers in China. CI, confidence interval; OR, odds ratio.

The PAF for lung cancer due to passive smoking

The pooled OR for lung cancer risk attributed to passive smoking in never smokers was 1.50 (95% CI: 1.35–1.67) (*Figure 2*), which was robust in the sensitivity analysis (*Figure S2*). However, heterogeneity was observed across the studies (I^2=60.4%, P<0.001) and there was some evidence of publication bias according to Begg's test (P=0.041) and an asymmetric funnel plot (*Figure S3*). The percentage of cases exposed to passive smoking was 61.6% (5,923/9,614), and the overall PAF for lung cancer due to passive smoking was 20.5% (95% CI: 15.9–24.9%).

The PAF for lung cancer due to passive smoking in population- and hospital-based studies

The pooled OR for passive smoking and lung cancer risk in never smokers was 1.36 (95% CI: 1.19–1.56) for the 9 population-based studies (*Figure 3*). Moreover, no heterogeneity was observed across the studies (I^2=0%, P=0.537), and there was no publication bias, as indicated by Begg's test (P=0.754) and a symmetrical funnel plot (*Figure S4*). In population-based studies, the PAF for lung cancer due to passive smoking was 15.5% (95% CI: 9.0–21.4%).

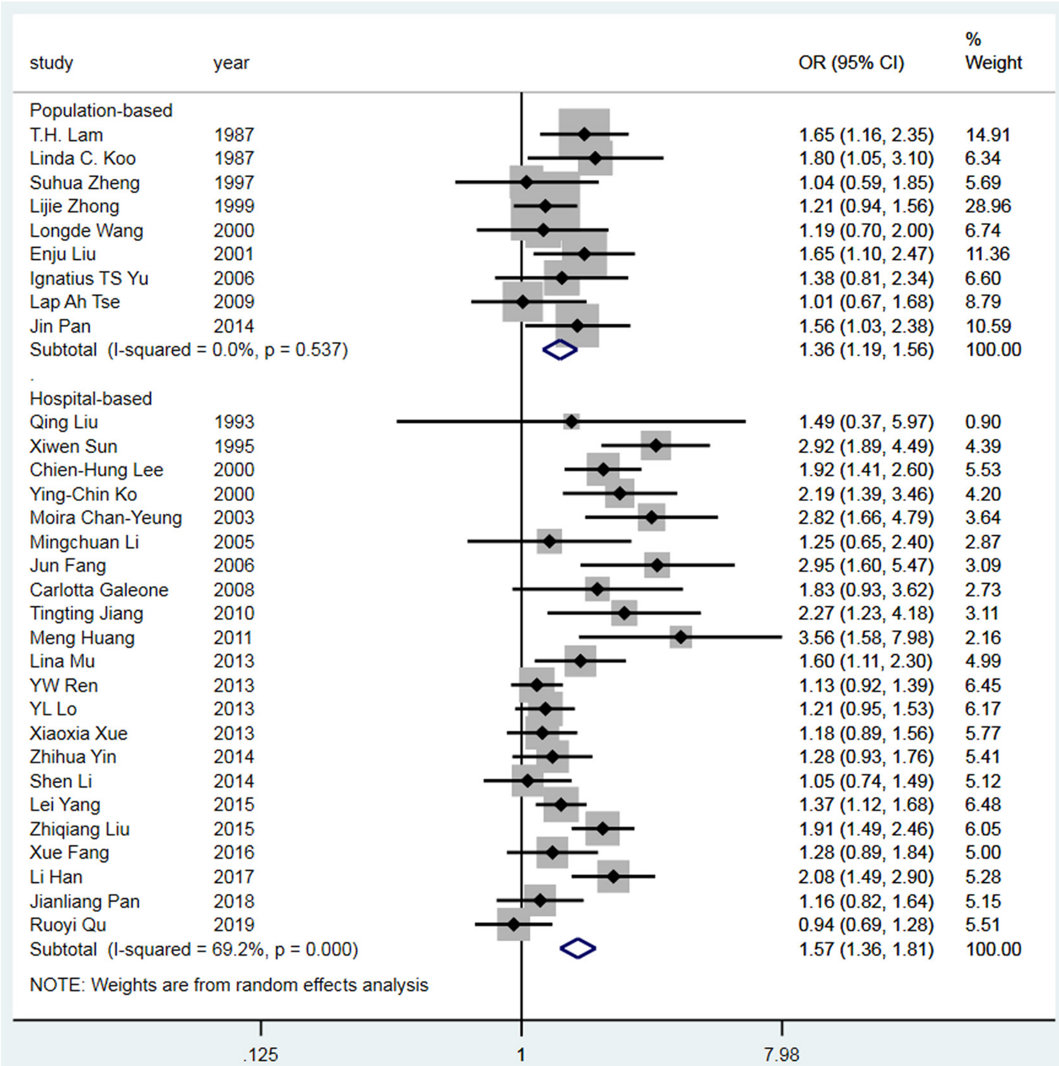

Figure 3 Forest plot of the random effects meta-analysis for the association between passive smoking and lung cancer among never smokers in China by study setting. CI, confidence interval; OR, odds ratio.

The pooled OR for passive smoking and lung cancer risk in never smokers was 1.57 (95% CI: 1.36–1.81) for the 22 hospital-based studies (*Figure 3*). However, substantial heterogeneity was observed (I^2=69.2%, P<0.001), and there was some evidence of publication bias, as indicated by Begg's test (P=0.048) and an asymmetrical funnel plot (*Figure S5*). In the hospital-based studies, the PAF for lung cancer due to passive smoking was 22.7% (95% CI: 16.6–28.3%) (*Table 2*).

The PAF for lung cancer due to passive smoking in men and women

For the population-based studies, the pooled OR for passive smoking and lung cancer risk in female never smokers was 1.45 (95% CI: 1.25–1.68), with no heterogeneity (I^2=0.0%, P=0.593) (*Figure S6*). The PAF for lung cancer due to passive smoking in this group was 17.9% (95% CI: 11.4–24.0%). The non-significant OR was yielded from the small number of population-based studies reporting the association between passive smoking and lung cancer risk in male never smokers meant that the PAF could not be estimated.

For the hospital-based studies, substantial heterogeneity was observed across studies (studies in females: I^2=65.0%, P<0.001; studies in males: I^2=77.2%, P=0.002) (*Figure S7*). The PAF for lung cancer due to passive smoking was 20.9%

Table 2 Population attributable fraction of lung cancer caused by passive smoking in never smokers

Study setting	No. of studies	NOS score	Cases	Cases exposed	Cases exposed (%)	Pooled OR	95% CI	I^2	P	PAF	95% CI
Population-based	9	6.4±1.0	2,172	1,268	58.4	1.36	1.19–1.56	0.0%	0.537	15.5%	9.0–21.4%
Women	8	6.4±1.1	1983	1,146	57.8	1.45	1.25–1.68	0.0%	0.593	17.9%	11.4–24.0%
Men	3	6.7±0.6	189	122	64.6	1.00	0.68–1.48	0.0%	0.755	–	–
Hospital-based	22	5.8±0.8	7,442	4,655	62.6	1.57	1.36–1.81	69.2%	<0.001	22.7%	16.6–28.3%
Women	19	5.8±0.8	5,946	3,731	62.8	1.50	1.31–1.73	65.0%	<0.001	20.9%	14.7–26.7%
Men	5	6.4±0.5	555	350	63.1	1.85	1.10–3.10	77.2%	0.002	29.0%	8.0–45.2%

CI, confidence interval; I^2, study heterogeneity; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PAF, population attributable fraction.

Table 3 Population attributable fraction of lung cancer caused by household and workplace passive smoking in female never smokers

Exposure source	No. of studies	NOS score	Cases	Cases exposed	Cases exposed (%)	Pooled OR	95% CI	I^2	P	PAF	95% CI
Household	8	6.5±0.9	2,606	1,720	66.0	1.42	1.21–1.67	40.8%	0.107	19.5%	11.4–26.9%
Workplace	6	6.8±0.8	2,379	465	19.6	1.58	1.33–1.88	0.0%	0.962	7.2%	4.6–9.7%

CI, confidence interval; I^2, study heterogeneity; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PAF, population attributable fraction.

(95% CI: 14.7–26.7%) in females and 29.0% (95% CI: 8.0–45.2%) in males (*Table 2*).

The PAF for lung cancer due to passive smoking in women, based on exposure source

The pooled OR for passive smoking at home and lung cancer risk among female never smokers was 1.42 (95% CI: 1.21–1.67), with no significant heterogeneity (I^2=40.8%, P=0.107) (*Figure S8*). The PAF for lung cancer due to passive smoking at home was 19.5% (95% CI: 11.4–26.9%). The pooled OR for passive smoking in the workplace and lung cancer risk among female never smokers was 1.58 (95% CI: 1.33–1.88), with no heterogeneity (I^2=0.0%, P=0.962). The PAF for lung cancer due to passive smoking in the workplace was 7.2% (95% CI: 4.6–9.7%) (*Table 3*).

The PAF for lung cancer due to passive smoking by histological type

The pooled OR for passive smoking and lung adenocarcinoma risk from the population-based studies was 1.58 (95% CI: 1.11–2.25), with no significant heterogeneity across studies (I^2=40.4%, P=0.169). The PAF for lung adenocarcinoma due to passive smoking was 28.2% (95% CI: 7.8–44.0%). PAF could not be estimated for the association between passive smoking and squamous cell carcinoma in never smokers because of the non-significant OR yielded from limited number of studies (*Table 4*, *Figure S9*).

Discussion

Main findings

We conducted a systematic review and meta-analysis based on evidence from nearly 23,000 participants in 31 studies. Our aim was to estimate the proportion of lung cancer cases that could be prevented by eliminating passive smoking in Chinese never smokers. Overall, using the PAF, we showed that approximately one-fifth of lung cancer cases were attributable to passive smoking, with a lower proportion from population-based studies (15.5%) than from hospital-based studies (22.7%). Given that population-based studies allow for more precise comparisons between cases and controls in a target population (53), data from these may have been more reliable (21). Furthermore, we demonstrated good homogeneity and no publication bias across the included population-based studies, indicating that the estimate from these data was unbiased. We conclude that the PAF estimate of 15.5% from population-based case-control studies was reliable. Regarding to the histological

Table 4 Population attributable fraction of lung cancer caused by passive smoking (subgroup analysis by histological type)

Histological type	No. of studies	NOS score	Cases	Cases exposed	Cases exposed (%)	Pooled OR	95% CI	I^2 (%)	P	PAF (%)	95%CI
All histological types	26	6.1±0.9	7,721	4,739	61.38	1.55	1.38–1.75	58.3	<0.001	21.8	16.8–26.5%
Population-based studies	8	6.4 ±1.1	1,674	1,196	71.45	1.33	1.15–1.53	0.0	0.539	17.7	9.2–25.4%
Hospital-based studies	18	5.9±0.8	6,047	3,543	58.59	1.67	1.43–1.96	66.5	<0.001	23.5	17.6–29.0%
Adenocarcinoma	10	6.2±1.0	2,509	1,651	65.80	1.48	1.18–1.86	66.0	0.002	21.3	10.3–31.0%
Population-based studies	4	7.0±0.8	559	429	76.74	1.58	1.11–2.25	40.4	0.169	28.2	7.8–44.0%
Hospital-based studies	6	5.7±0.8	1,950	1,222	62.67	1.44	1.07–1.95	75.5	0.001	19.1	4.7–31.4%
Squamous cell carcinoma	3	6.7±0.6	101	57	56.44	1.36	0.80–2.32	0.0	0.400	–	–

CI, confidence interval; I^2, study heterogeneity; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PAF, Population attributable fraction.

type of lung cancer, compared to the studies including all histological types, the proportion of lung adenocarcinoma caused by passive smoking in never smokers was higher (28.2% *vs.* 17.7%) based on the population-based studies.

The proportion of lung cancer cases that could be prevented among women by stopping passive smoking was 18% in this study, which was lower than the 24% reported in a previous estimate from 2008 (54). However, the RR of passive smoking for lung cancer was comparable with that in the previous publication, implying that there has been an overall decrease in the prevalence of passive smoking. This could be because China officially signed the Framework Convention on Tobacco Control in 2003 (55), which has resulted in several smoke-free policies being implemented (56-58). Additional positive effects on lung cancer occurrence can be expected from these measures because smoking rates decline slowly. The risk of lung cancer in exposed individuals may therefore decline further over time as exposure to passive smoking reduces.

The overall proportion of lung cancers attributable to passive smoking in Chinese never smokers (16%) was similar to that estimated for the United Kingdom (14–15%) in 2010 (59). However, it was much higher than that reported for the United States in 2014, where passive smoking contributed to only 2.7% of lung cancers (3.1% for men, 2.3% for women) in both never and ever smokers (60). The prevalence of smoking in the United States has decreased over several years (61), and it has been reported that the prevalence of passive smoking in nonsmokers was only 25.2% in 2014 (62). In the present study, the PAF for female never smokers for China (18%) was close to that estimated for Korea in 2009 (20.7%) (63) and Japan in 2005 (18.9%) (64). By contrast, in France, 6.7% of female lung cancers were attributable to domestic passive smoking, a rate that is much lower than reported for female never smokers in China (65). This could be due to the comparatively higher prevalence of passive smoking in China. Indeed, according to surveys in 2015, exposure to passive smoking in the home among female never smokers was 51.4% in China (10), whereas it was reported to range from 2.9% to 42.8% (increasing with age) in France (65).

The proportion of lung cancers attributable to passive smoking in the home (19.5%) was much higher than that in the workplace (7.2%) among women. The main reason for this appeared to be that more women were exposed to passive smoking in the home (66.0%) than in the workplace (19.6%). According to a survey of adults aged ≥40 years in China, 37.7% of never smokers exposed to passive smoking reported that they were usually exposed at home, whereas only 7.1% reported that they were usually exposed in the workplace (14). The home is therefore the predominant site of exposure to passive smoking, especially for women and children (12). One study indicated that this may reflect a displacement effect due to smoke-free legislation, with the net effect being that people smoke more frequently at home to avoid the restrictions in place at public places (66). As a priority, we therefore recommend that public health policy in China aim to reduce passive smoking in the home.

Limitations

Estimating the PAF in a systematic review and meta-analysis is an alternative approach when data on exposure rates are not available from national surveys. However, there are some limitations in the study. First, we used the OR from case-control studies as an approximation of the RR because there were no eligible cohort studies. Although this is not ideal, the OR from a case-control study is considered a valid substitute for the RR from a cohort study when a disease is uncommon (16). Second, we could not control for the effects of cooking fumes when estimating the PAF of lung cancer due to passive smoking in the home, which might have resulted in an overestimation of the PAF. Third, most of the studies had no blinding to the case/control status during interview, indicating a possible high risk of information or misclassification bias. Fourth, the PAF for male never smokers could not be estimated because there were insufficient population-based studies.

Conclusions

The results of this review and meta-analysis indicate that passive smoking contributes to about 16% of lung cancers in Chinese never smokers, but that this increases to 18% in females. Further measures are needed to control against the harmful effects of passive smoking, especially in Chinese women, and we recommend that public health efforts should prioritize reducing levels of passive smoking in the home. It appears that the biggest gains can be achieved here, not only by preventing lung cancer but also by preventing other diseases associated with passive smoking.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr.2020.02.11). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Database search strategy

Database	Search strategy
PubMed	((“Lung Neoplasms” [Mesh] OR ((lung[tiab] OR lungs[tiab] OR pulmonary[tiab]) AND (cancer*[tiab] OR neoplasm* OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab]))) AND (“Tobacco Smoke Pollution” [Mesh] OR (smok*[tiab] AND (second-hand[tiab] OR secondhand[tiab] OR passive[tiab] OR involuntary[tiab] OR environmental[tiab] OR expos*[tiab]))) AND (“China”[Mesh] OR “Taiwan” [Mesh] OR China [tiab] OR Chinese [tiab] OR Taiwan* [tiab])) NOT (“Animals”[Mesh] NOT “Humans”[Mesh])
Web of Science (core collection)	(TS=((lung OR lungs OR pulmonary) AND (neoplasm* OR cancer* OR tumo* OR carcinoma* OR adenocarcinoma*))) AND (TS=(Smok* AND (secondhand OR second-hand OR passive OR involuntary OR environmental))) AND (TS=(China OR Chinese OR Taiwan))
China National Knowledge Infrastructure (in Chinese)	(SU= ‘lung cancer’ OR SU= ‘lung adenocarcinoma’ OR SU= ‘squamous cell lung carcinoma’ OR SU= ‘malignant tumor of lung’) AND (SU= ‘secondhand smoke’ OR SU= ‘passive smoking’ OR SU= ‘environmental tobacco smoke’ OR SU= ‘indirect smoking’)
Wan Fang database (in Chinese)	(“lung cancer”+”lung adenocarcinoma”+”squamous cell lung carcinoma”+”malignant tumor of lung”) * (“secondhand smoke”+”passive smoking”+”environmental tobacco smoke”+”indirect smoking”)
Database of Chinese Scientific & Technical Periodicals (in Chinese)	(M=lung cancer OR M=lung adenocarcinoma OR M=squamous cell lung carcinoma OR M=malignant tumor of lung OR R= lung cancer OR R=lung adenocarcinoma OR R=squamous cell lung carcinoma OR R=malignant tumor of lung) AND (M=secondhand smoke OR M=passive smoking OR M=environmental tobacco smoke OR M=indirect smoking OR R=secondhand smoke OR R=passive smoking OR R=environmental tobacco smoke OR R=indirect smoking)
China Biology Medical literature database (in Chinese)	(“lung cancer”[title] OR “lung adenocarcinoma”[title] OR “squamous cell lung carcinoma”[title] OR “malignant tumor of lung”[title] OR “lung cancer”[abstract] OR “lung adenocarcinoma”[abstract] OR “squamous cell lung carcinoma”[abstract] OR “malignant tumor of lung”[abstract]) AND (“secondhand smoke”[title] OR “passive smoking”[title] OR “environmental tobacco smoke”[title] OR “indirect smoking”[title] OR “secondhand smoke”[abstract] OR “passive smoking”[abstract] OR “environmental tobacco smoke”[abstract] OR “indirect smoking”[abstract])

Table S2 Matched and adjusted factors of overall odds ratios in the included studies

Study	Study population	Overall OR derivation	Matched factors in study design	Adjusted confounders in data analysis
TH Lam 1987	Women	Extracted	Age, place of residence	No
LC Koo 1987	Women	Calculated[††]	Age, district of residence, housing type	Age, number of live births, schooling, years since exposure to cigarette smoke ceased in the home or workplace
Q Liu 1993	Women	Calculated[‡]	Age, residential district, date of diagnosis or hospital admission	Education, occupation, living area
X Sun 1995[†]	Women	Extracted	Not provided	Age, education
S Zheng 1997[†]	Women + Men	Extracted	Age, sex	No
L Zhong 1999	Women	Calculated[‡‡]	Age	Age, income, intake of vitamin C, respondent status, smokiness of the kitchen during cooking, family history of lung cancer, and potentially high-risk occupations
L Wang 2000	Women + Men	Extracted	Age, sex, prefecture	Sex
CH Lee 2000	Women	Calculated[§]	Age	Residential area, education, occupation, tuberculosis, cooking fuels and fume extractor
YC Ko 2000	Women	Calculated	Age	No
E Liu 2001[†]	Women	Extracted	Age	Age, monthly income
YM Chan 2003	Women + Men	Calculated[§§]	Age, sex	Place of birth, educational status, a family history of lung cancer, history of tuberculosis, exposure to insecticide/pesticide, diet
M Li 2005[†]	Women	Calculated	Age	No
IT Yu 2006	Women	Calculated	Age	No
J Fang 2006[†]	Women	Extracted	Age	No
C Galeone 2008	Women + Men	Extracted	Age, sex, area of residence	Income, family history of lung and other cancers, occupational exposure to recognized lung carcinogens
LA Tse 2009	Men	Extracted	Age	Age, place of birth, alcohol drinking, residential radon exposure, past history of lung diseases, any cancer in first-degree relatives, intakes of meat, exposure to known or suspected lung carcinogens, and adoption of dust control
T Jiang 2010[†]	Women + Men	Extracted	Age, sex	BMI, lived nearby (≤3 km) factories, moved into newly renovated homes, Family cancer history, history of lung disease, regular consumption of soy foods, eating fruit and vegetable, regular participating in physical exercise, mental and psychological, heavy work pressure factors, sleep quality
M Huang 2011[†]	Women + Men	Calculated[¶]	Age, sex	Age, sex, ethnic, education, BMI
L Mu 2013	Women + Men	Extracted	Age, sex	Age, education level, annual personal income
YW Ren 2013	Women	Extracted	Age	No
YL Lo 2013	Women + Men	Calculated[¶¶]	Age, sex, ethnic	Age, years of education. For women additionally adjusted for family history of lung cancer, tuberculosis, fume extractor in kitchen, hormone replacement therapy
X Xue 2013	Women	Calculated	Age	No
Z Yin 2014	Women	Extracted	Age	Age
S Li 2014	Women	Calculated	Age	No
J Pan 2014[†]	Women	Extracted	Age, cancer history, residence years	No
L Yang 2015	Women + Men	Extracted	Age, sex	Age, sex, BMI, educational experience, study center, and pre-existing tuberculosis, pre-existing emphysema, occupational exposure to metallic toxicant, housing ventilation, biomass burning, cured meat consumption, vegetables/fruits consumption
Z Liu 2015[†]	Women + Men	Extracted	Age, sex	Age, sex, education, BMI
X Fang 2016	Women	Calculated	Age	No
L Han 2017	Women + Men	Calculated	Age, sex	No
J Pan 2018	Women	Calculated	Age	No
R Qu 2019	Women	Calculated	Age	No

[†], study published in Chinese language; [††], overall OR was calculated by pooling OR for "1–19", "20–34", "35+" exposure years in this article; [‡], overall OR was calculated by pooling OR for "1–19", "≥20" exposed cigarettes smoked per day by husband in this article; [‡‡], overall OR was calculated by pooling OR for childhood only, adulthood only and both ages in this article; [§], overall OR was calculated by pooling OR for different groups of smoker-year in this article; [§§], overall OR was calculated by pooling OR for men and women in this article; [¶], overall OR was calculated by pooling OR for light and heavy exposure in this article; [¶¶], overall OR was calculated by pooling OR for household and workplace exposure in men and household and workplace exposure in women in this article. OR, odds ratio.

Table S3 Quality assessment of the eligible studies for systematic review and meta-analysis

Author	Year	Selection (4 stars)	Comparability (2 stars)	Exposure (3 stars)
TH Lam	1987	****	*	**
LC Koo	1987	***	*	*
Q Liu	1993	***	*	**
X Sun†	1995	***	*	*
S Zheng†	1997	****	*	*
L Zhong	1999	****	**	**
L Wang	2000	****	*	**
CH Lee	2000	***	**	**
YC Ko	2000	***	*	**
E Liu†	2001	****	*	**
M Chan-Yeung	2003	***	**	*
M Li†	2005	***	*	*
IT Yu	2006	***	*	*
J Fang†	2006	***	*	*
C Galeone	2008	***	**	*
LA Tse	2009	****	**	*
T Jiang†	2010	***	**	**
M Huang†	2011	***	*	*
L Mu	2013	***	*	**
YW Ren	2013	***	*	*
YL Lo	2013	***	**	**
X Xue	2013	***	*	**
Z Yin	2014	***	*	*
S Li	2014	***	*	**
J Pan†	2014	****	*	*
L Yang	2015	****	**	*
Z Liu†	2015	***	*	**
X Fang	2016	***	*	*
L Han	2017	***	*	*
J Pan	2018	***	*	**
R Qu	2019	***	*	*

Performed using the Newcastle-Ottawa Scale (NOS), one star (*) was awarded if the rating item was met. †, study published in Chinese language.

Table S4 Definition of never smoker and passive smoking across the included studies

Author	Year	Definition of never smoker	Definition of passive smoking
TH Lam	1987	One who had never smoked as much as one cigarette a day or equivalent for the duration of one year	A woman was considered exposed to her husband's tobacco smoke if she had lived together with her smoking husband in the same household for at least one year continuously
LC Koo	1987	Never-smoked subjects were defined as those who had smoked less than 20 cigarettes in the past	NA
Q Liu	1993	NA	NA
X Sun	1995	NA	NA
S Zheng	1997	NA	NA
L Zhong	1999	NA	NA
L Wang	2000	Never smoked cigarettes or pipes regularly for 6 months or longer	NA
CH Lee	2000	People who did not smoke as much as one cigarette per day for one year, or 365 cigarettes over their lifetime were considered lifetime non-smokers	Passive smoker was identified as a patient whose family members had smoked in her "presence," as some Chinese smokers do not smoke at home in the presence of their family
YC Ko	2000	A nonsmoker was defined as a woman who had never smoked one cigarette during her lifetime	Subjects who lived or worked with a smoker during their childhood and adulthood, such as a parent, husband, cohabitant, or coworker, were considered passive smokers
E Liu	2001	NA	NA
Moira Chan-Yeung	2003	NA	Life-long nonsmoker exposed to anyone who smoked at home or workplace regularly for at least 2 years
M Li	2005	NA	NA
IT Yu	2006	NA	Ever lived or worked with a smoker for at least 1 year and was regularly exposed to tobacco smoke
J Fang	2006	Consumed less than 100 cigarettes in total or smoked less than 6 months	NA
C Galeone	2008	NA	NA
LA Tse	2009	A non-smoker was defined as one who had never smoked as many as 20 packs of cigarettes or 12 ounces (340.2 g) of tobacco in his lifetime or 1 cigarette a day or 1 cigar a week for 1 year	Ever lived or worked with a smoker for at least 1 year and was regularly exposed to tobacco smoke
T Jiang	2010	NA	NA
M Huang	2011	NA	Exposed to the anyone's tobacco smoke for more than 15 minutes per day
L Mu	2013	NA	NA
YW Ren	2013	Those who had consumed as much as one cigarette per day for 1 month in their lifetime were defined as smokers, otherwise they were considered as nonsmokers	Passive smokers if they were exposed to the smoke from more than one cigarette per day for at least 1 year
YL Lo	2013	A never smoker was defined as someone who had never smoked or not smoked 1 cigarette a day or 1cigarette a week for 6 months at any period during his/her lifetime	Subject's regular exposure to tobacco smoke by living or working with a smoker.
X Xue	2013	An individual was defined as a smoker if she had consumed a total of 100 cigarettes in her lifetime; otherwise, she was considered as a non-smoker	NA
Z Yin	2014	Individual with a total of 100 cigarettes in his lifetime was defined as a smoker; otherwise, he was considered as a non-smoker	NA
S Li	2014	An individual was defined as a smoker if she had consumed a total of 100 cigarettes in her lifetime; otherwise, she was considered as a non-smoker	NA
J Pan	2014	Someone who had never smoked or not smoked 1 cigarette a day or smoked less than 6 months	NA
L Yang	2015	Those participants who had smoked <100 cigarettes in their lifetime were defined as never smokers	NA
Z Liu	2015	Consumed less than 100 cigarettes in total	Nonsmoker exposed to tobacco smoke for at least 1 day per week (more than 15 minutes per day)
X Fang	2016	In their lifetime, subjects who had smoked less than 100 cigarettes were defined as non-smokers	Individuals who had been exposed to the secondhand smoke of one cigarette every day for at least one year were defined as passive smokers
L Han	2017	Who had never smoked or had smoked fewer than 100 cigarettes during their lifetime	NA
J Pan	2018	Persons consuming 1 or more cigarettes per day for more than 1 month or if the cumulative amount reaches this level during a short period of Time were excluded from the study	Subjects exposed to 1 or more cigarettes per day for a period of more than 1 year.
R Qu	2019	Individuals having a total of 100 cigarettes in their entire life were defined as smokers, otherwise as nonsmokers	Passive smokers were subjects who were exposed to more than one cigarette smoke per day for at least 1 year

NA, not available.

Items	Content		Notes
Basic information			
Title			
First author			
Year of Publication			
Journal			
Aim of the study			
Methods			
Study design (n:n matched) case-control study, Prospective/ Retrospective cohort study			
Study population (male/female/both)			
Study period			
Setting (population-based /hospital-based study)			
Definition of non-smoker			
Region			
Cases (or outcome in case of cohort study)			
Source of lung cancer cases			
Diagnostic criteria for lung cancer			
In- and exclusion criteria of lung cancer			
Type of lung cancer			
Response rate			
Event (incidence/death)			
Controls			
Source of controls			
In- and exclusion criteria of controls			
Passive smoking			
Definition of PS			
In- and exclusion criteria of PS exposure (in case of cohort study)			
Sources of PS			
Exposure Period (childhood/adulthood)			
Results			
Sample size			
Follow-up (years) (in case of cohort study)			
No. of loss to follow up (in case of cohort study)			
Age (mean ± SD/range)			
Table for overall	No. of cases	No. of controls	
No. of PS			
No. of non-PS			
Table for female	No. of cases	No. of controls	
No. of PS			
No. of non-PS			
Table for male	No. of cases	No. of controls	
No. of PS			
No. of non-PS			
Crude OR/RR and 95% CI			
Adjusted OR/RR and 95% CI			
Adjusted confounding factors			
Conclusion			

Figure S1 Data extraction form. Note: more tables can be added if needed. CI, confidence interval; OR, odds ratio; PS, passive smoking; RR, relative risk.

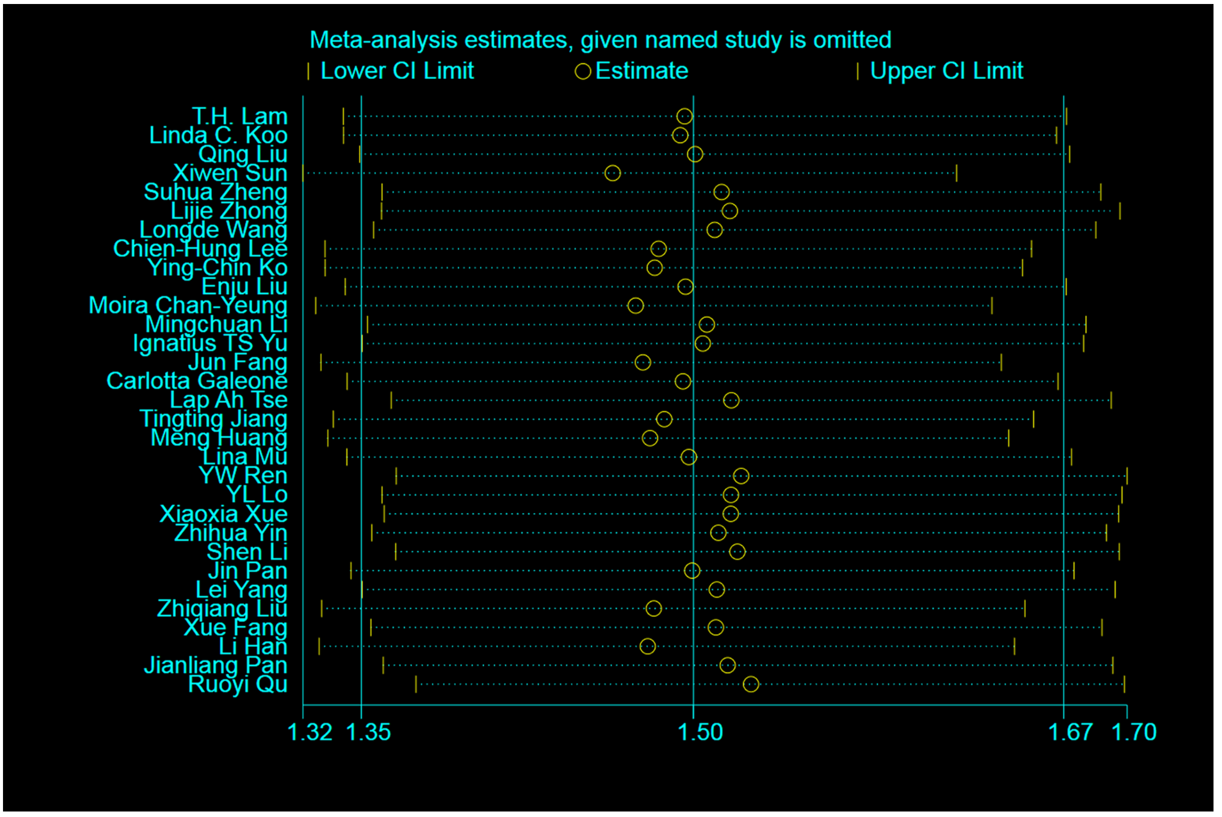

Figure S2 Sensitivity analysis for the association between passive smoking and lung cancer risk among never smokers in China.

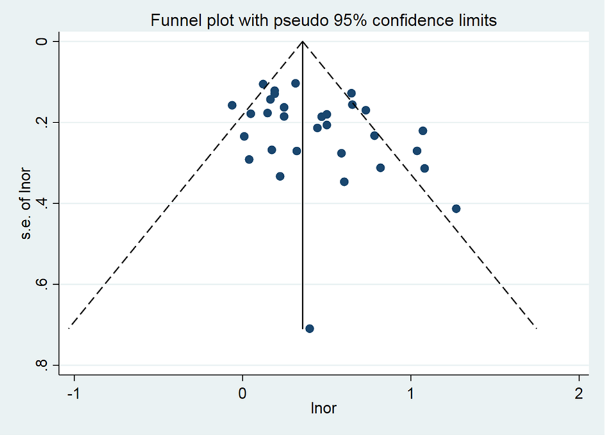

Figure S3 Funnel plot of publication for the association between passive smoking and lung cancer risk among never smokers in China.

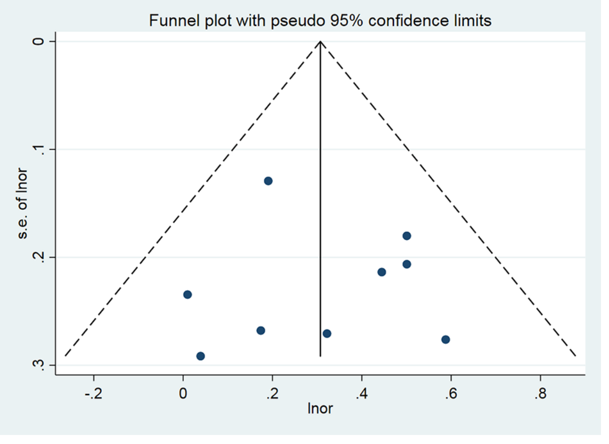

Figure S4 Funnel plot of possible publication bias in population-based studies. Data are for the association between passive smoking and lung cancer risk among never smokers in China.

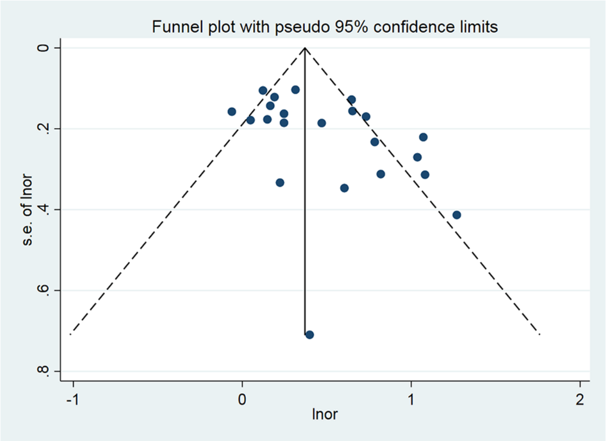

Figure S5 Funnel plot of possible publication bias in hospital-based studies. Data are for the association between passive smoking and lung cancer risk among never smokers in China.

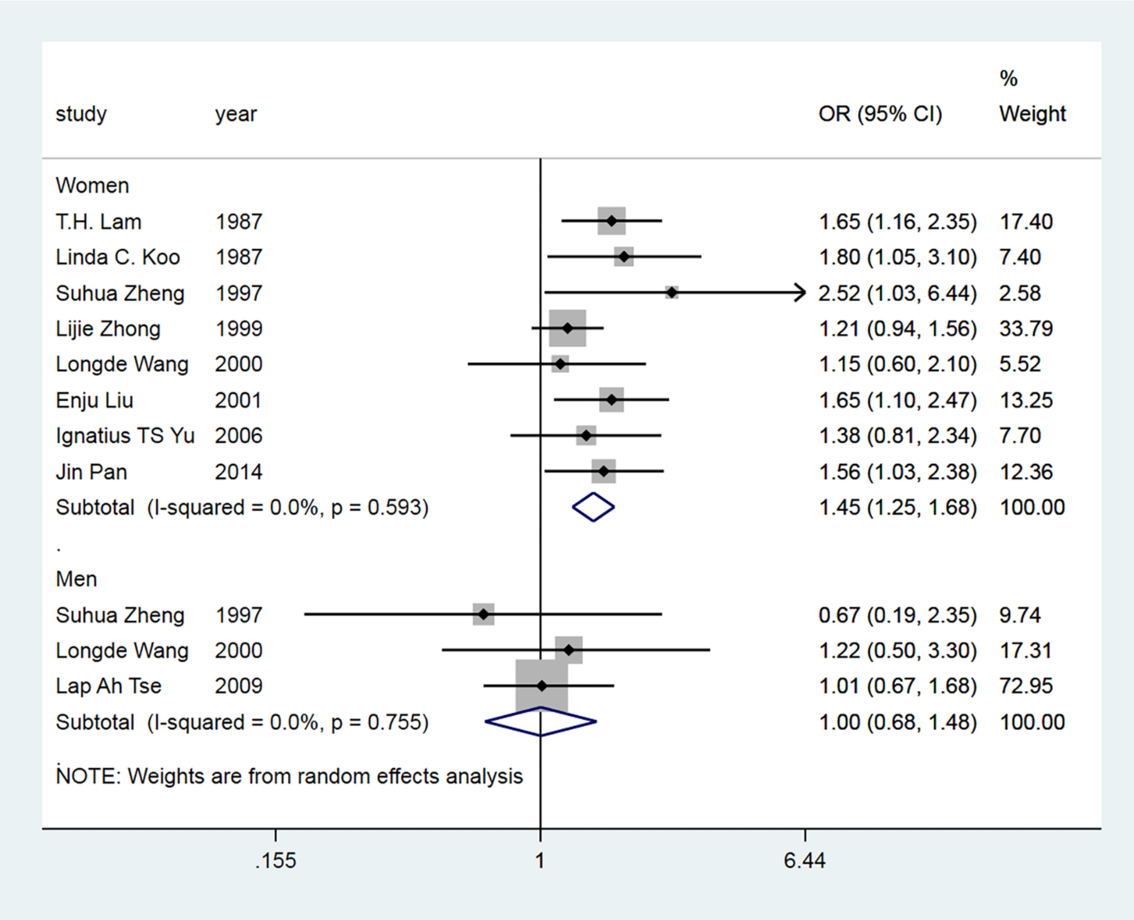

Figure S6 Forest plot of the random effects meta-analysis in population-based studies. Data are for the association between passive smoking and lung cancer risk among never smokers for women and men in China. CI, confidence interval; OR, odds ratio.

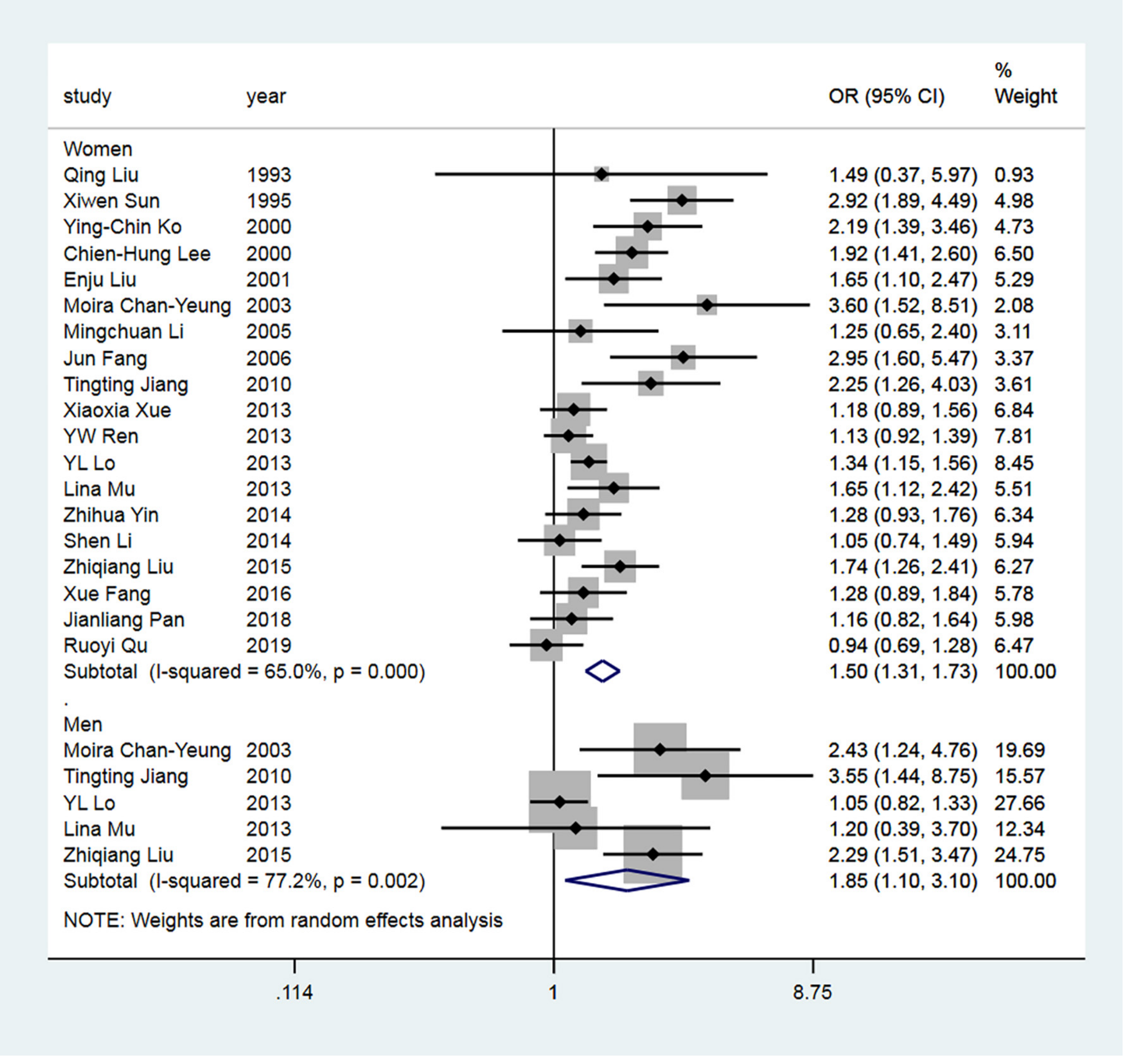

Figure S7 Forest plot of the random effects meta-analysis in hospital-based studies. Data are for the association between passive smoking and lung cancer risk among never smokers for women and men in China. CI, confidence interval; OR, odds ratio.

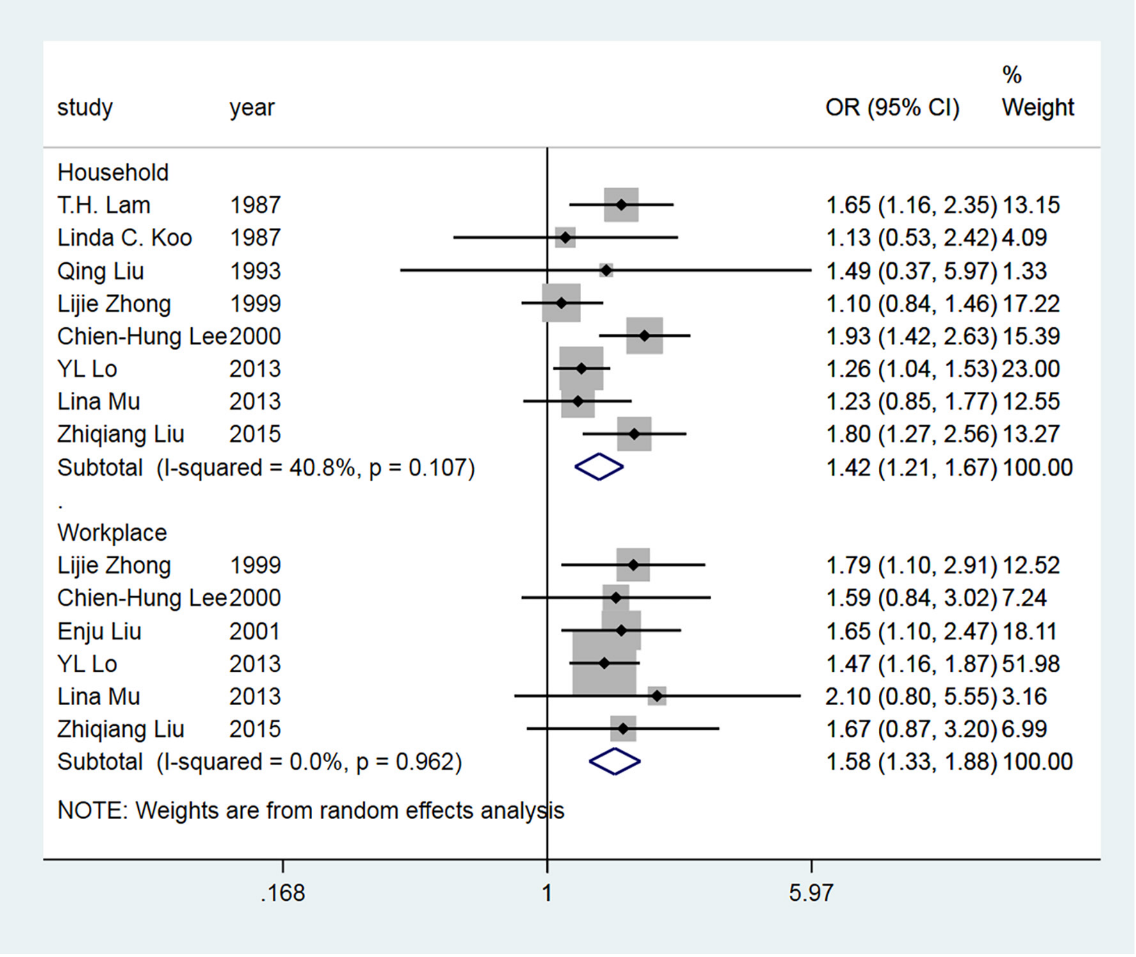

Figure S8 Forest plot of random effects meta-analysis for the association between passive smoking and lung cancer among female never smokers by exposure source in China. CI, confidence interval; OR, odds ratio.

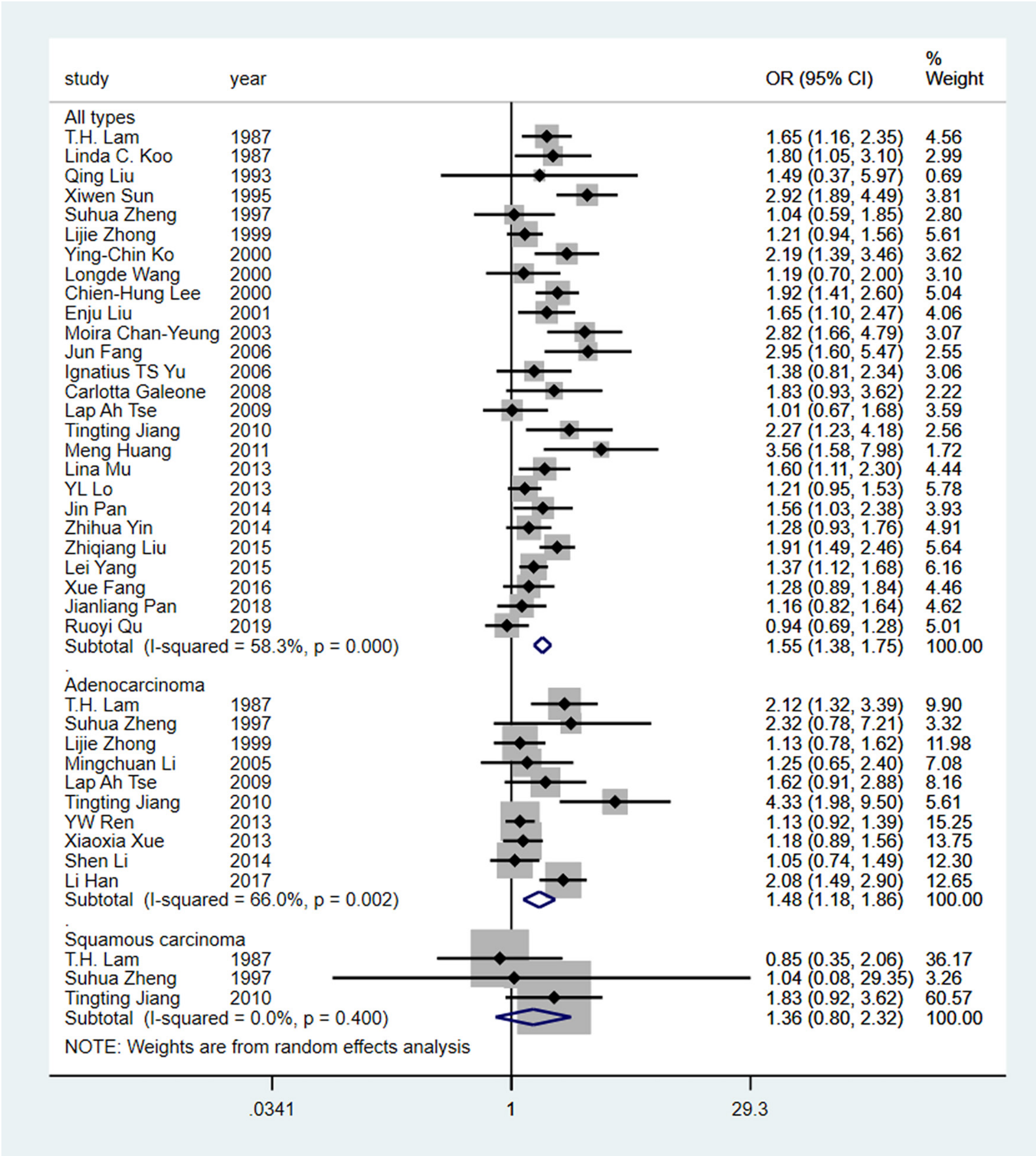

Figure S9 Forest plot of random effects meta-analysis for the association between passive smoking and lung cancer among never smokers by histological type in China. CI, confidence interval; OR, odds ratio.